

Name and Address of Sponsor/Company: Inozyme Pharma 321 Summer St Floor 4 Boston MA 02210
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Amendment Number and Date, If Applicable: Not applicable
Name of Investigational Product: Not applicable
Title of Study: Understanding the Spectrum of ENPP1 Deficiency and Acute ABCC6 Deficiency Through the Eyes of Patients and Parents; Burden of Illness Perspectives from Patients and Parents who Speak English, French or German
Phase of development: Not applicable
Background: <p>ENPP1 deficiency is a systemic and progressive disorder with high morbidity and mortality. Biallelic, loss of function mutations in the ENPP1 gene, which encodes the ENPP1 enzyme, cause ENPP1 deficiency. In rare cases, biallelic mutations in the ABCC6 gene which encodes the ABCC6 transporter cause a disorder resembling the acute infantile form of ENPP1 deficiency. Both proteins produce extracellular pyrophosphate (PPi), a key regulator of mineralization, directly (ENPP1) or indirectly (ABCC6). The condition leads to pathological mineralization of arteries and arterial neo-intimal proliferation; calcification of joints and organs; organ dysfunction; hypophosphatemia rickets; short stature; developmental and cognitive delays; osteomalacia; pain and poor quality of life.</p> <p>ENPP1 deficiency and the acute form of ABCC6 deficiency present as a continuum of progressive signs and symptoms throughout life. ENPP1 deficiency and ABCC6 deficiency share an acute infantile phase characterized by ectopic calcification of the major arteries leading to high mortality from major cardiovascular events MI, CVA, AS, etc.). Pediatric subjects surviving this phase go on to develop morbid complications of disease, including</p>

phosphate wasting and the development of rickets. Adults with ENPP1 deficiency experience organ and tissue calcification, physiological deterioration, and significant morbidity.

Hypopyrophosphatemia (low pyrophosphate [PPi]) is pathognomonic of ENPP1 deficiency, and may explain the acute form of ABCC6 deficiency, throughout all of its phases. This key biochemical defect in patients drives the progression of all the known pathologic calcification disorders found in all stages of the disease.

To date, we lack characterization of, the burden of, and the systemic progression of disease in ENPP1 deficiency and ABCC6 deficiency from a patient and/or parent perspective. This study aims to document this characterization, progression as well as the burden of disease.

Note: Historically, alternate terminology was used that referred to ENPP1 deficient patients as having GACI Type 1 and ABCC6 deficient patients as having GACI Type 2. Additionally, many patients who survive GACI go on to develop ARHR2, which is usually associated with the ENPP1 gene. Because many patients impacted by ENPP1 or ABCC6 deficiency were diagnosed using these alternate terms, all patient-facing materials in the study utilize the terms GACI and ARHR2 as well as ENPP1 or ABCC6 deficiency.

Objectives:

- To improve the understanding of the characterization and burden of disease in ENPP1 deficient, and acute ABCC6 deficient, patients who are still growing and those who are done growing
- To collect information regarding disease burden, in the patient's / families own terms
- To build a foundation of evidence to contribute to the dossier, used for many purposes, including reimbursement and regulatory bodies.

Study Design:

This will be a comprehensive, cross-sectional study conducted in approximately 60 individuals (or representative parents of patients) affected by ENPP1 deficiency and the acute form of ABCC6 deficiency. All study participants will complete the RSVP, PRO tools and upload a proof of disease form, followed by an interview conducted by a trained interviewer. It is estimated that each respondent will need up to 60 minutes for the entire process; 20 minutes to complete the RSVP, PRO tools and to upload proof of diagnosis of ENPP1 deficiency or the acute form of ABCC6 deficiency, and approximately 40 minutes to complete the interview and address any follow-up questions if needed.

Study Methods (see Appendix A)**Roles**

The study will be sponsored by Inozyme. Study design and questions were developed with input from clinical experts, Inozyme's Chief Medical Officer, Pedro Huertas, MD, PhD, and Christine O'Brien, Co-President of GACI Global (the disease patient support organization), Engage Health (a health research firm), and representatives of Inozyme. Engage Health will conduct interviews and perform statistical analysis. Central IRB approval will be obtained prior to the initiation of the study.

Recruitment and Recruitment Materials (see Appendix B)

Participants will be recruited in territories where individuals speak English, German or French (these are likely to be Germany, France, the UK, Canada, Australia and the U.S.) from various sources including GACI Global, social media, and from Engage Health's proprietary EnCompass® database, in which patients have opted in to be notified of research opportunities. Sample recruitment materials (text only) including email outreaches and social media posts are provided in Appendix B of this document. A web page that describes the study can be found in Appendix C of this document. The researchers will seek to recruit 60 participants across four groups; person or parent/legal guardian affected by ENPP1 (GACI or ARHR2) or the acute form of ABCC6 deficiency as described below;

- Acute infantile ENPP1 deficiency (note; due to the high infant mortality, this group is likely to include parents of affected children, both living and deceased)
- Acute infantile ABCC6 deficiency (note; due to the high infant mortality, this group is likely to include parents of affected children, both living and deceased)
- Progressive pediatric ENPP1 deficiency who are still growing (note; due to the age of those who are still growing, this group is likely to include parents of affected children)
- Adult ENPP1 deficiency who are no longer growing (note: due to the age of those who are no longer growing, this group is likely to include both patients \geq age 18 years and parents of affected children who are $<$ age 18 years or who are unable to answer for themselves)

Consent and Assent (see Appendix D)

Each interested individual will visit an on-line RSVP site and complete an online informed Consent form to participate in the study. If a person is under the age of 18 and would like to participate in the PRO portion of the study, they will be asked to fill out the

online Assent. If the individual has research-related questions about the study, the individual will be directed to Dr. Pedro Huertas at (978) 394-5700, who will answer the questions. A copy of the signed and dated informed consent/assent can be printed from the site by the participant.

RSVP Survey and Interview Data (see Appendix E)

After the consent/assent is signed, the individual will provide answers to demographic questions, including ethnicity, Personal Data (which will be used to schedule the telephone interview) including name, telephone number, email address, and address. Personal information is required for purposes of setting up the interview, conducting the interview and paying honoraria. The email address and telephone number may also be used for data clarification if necessary (see Quality Control). They will also provide age in months and years of the person impacted by ENPP1 or ABCC6 deficiency. Based on the age, they will see age-appropriate validated tools: Ages and Stages Questionnaire TM; PedsQL TM or PROMIS [®]; participants and caregivers for those over age three years will see the Brief Pain Inventory. These will be printed by the participant, filled out manually, and uploaded to the site.

Each respondent will provide "proof of disease" (such as genetic diagnosis from a relevant testing laboratory, physician consult notes, school note describing accommodations and disease name, or medical record of diagnosis) by uploading it to the site, and will denote times that will work for them to participate in the telephone interview. If there is difficulty uploading the completed PRO forms or proof of disease, study participants will complete the RSVP, and the staff of Engage Health will contact them in order to assist with any technological difficulties.

Interview

Following informed consent/assent, confirmation of diagnosis of ENPP1 deficiency or the acute form of ABCC6 deficiency, and group assignment based on disease and growth status (e.g. still growing or no longer growing), study participants will be scheduled for a 40 to 60-minute interview administered via telephone by trained interviewers, conducted in their native language or in English (language is selected by the participant). During the interview, the interview staff will enter the respondent's answers to the questions to Engage Health's proprietary, HIPAA compliant study module. As part of this process, the information provided in the RSVP disease and growth status will drive "skip logic" in order to ensure that questions will only be asked of participants to whom they pertain. If the participant does not wish to answer any question in the study, they will be given the option to abstain. If the participant wishes to discontinue the study, they will be allowed

to stop at any time. If the participant agrees, the interview will be recorded and stored in a pseudonymized fashion as an MP3 file in Engage's proprietary, HIPAA compliant servers.

Participants will be asked, in an un-aided fashion, about key burdens related to their/their child's disease, as well as the life impacts of those burdens for the patient and family. All of the respondent's answers are considered "Anonymous Data".

Remuneration

At the completion of each interview, the participants will be paid \$100 honoraria. A choice will be given for the participant to select a \$100 check paid in US dollars and mailed by Engage Health, or an e-gift card to Amazon.com sent by email by Engage Health.

Discontinuation of a participant

Engage Health, Inc., the health research vendor, or the sponsor may discontinue the participant if it is in the participant's best interest, the participant does not consent to potential changes made in the study plan (if applicable), or the participant does not keep the scheduled appointment for the telephone interview.

Quality Control (QC)

At the completion of the interviews, the data will be reviewed for clarity and completeness, and interview tapes will be accessed if the participant consented to recording. If there is a need for additional information, the participant will be contacted by Engage Health to clarify the data. Any data that is not able to be clarified will be flagged as an outlier and that data will not be available for analysis.

At the completion of the QC, Engage Health will download all Study Data (the combination of Personal Data and Anonymous Data) and pseudonymize the Personal Data, removing all identifying information and assigning each patient a unique identifier. The log of unique identifiers will be stored separately from the anonymized data. When this is completed, the database will be locked.

Analytic Plan

As described above the pseudonymized answers provided by each respondent will be combined with those of others participating in the study and the pseudonymized database

(Excel format) will be locked and provided to Engage Health personnel for analysis (“Study Data”). The goal of the thematic analysis is to uncover patterns and trends that provide both evidence and context for experiences and disease burdens reported by patients and families impacted by ENPP1 deficiency (GACI or ARHR2) or the acute infantile form of ABCC6 deficiency.

In this analysis the combination of an inductive and deductive approach will be used to assess each study subgroup

- Inductive Approach: First, each participant will be asked about the burden of access to them/their child, as well as the life impact. Information will be gathered in the words of the participant.
 - At the conclusion of the interviews, the information will be assessed from a latent perspective, with two independent coders reviewing the comments, subtext and related discussion to determine the theme. If there is not agreement between the coders. A third party trained in coding will independently assess and make a determination.
 - In order to ensure data is representative, the study will ensure saturation of themes for each subgroup. To do this, the first 5 respondents in each subgroup will be considered the baseline group. Recruitment will be purposive with each subsequent group of five considered a cohort.
 - The first cohort will be compared to the baseline; if any themes are raised that were not raised by the baseline group, saturation will not have been met, and recruitment will continue.
 - The second cohort will be compared to the baseline group plus the first cohort, if any themes are raised that were not raised by the baseline group, saturation will not have been met, and recruitment will continue.
 - The sponsor intends to recruit as many patients as possible to fully understand the burden of disease. However, given the rarity of these conditions, recruitment *may* end when the subgroup cohort does not raise any new themes that are meaningful and important compared to the previous groups.
- Deductive Approach: Prior to the interviews a list of burdens that are expected from each group will be compiled by the research team and will be reviewed by the participant *after* the questions are asked in an un-aided way. This will allow the participant to review the list and provide a different answer, information

about participants who changed their answer will be described as a descriptive statistic.

All findings will be summarized in the final report, which will not identify any respondent as described above. At the conclusion of this study, the researchers may publish their findings in a medical / scientific journal.

Data Collection and Storage

The following procedures will be used to protect the confidentiality of study data.

The RSVP information will be entered by the study participant into the RSVP site. Validated questionnaires will be printed and filled out by the participant. These, along with the “Proof of Disease Form” will be uploaded or otherwise provided to Engage Health. The interview data will be entered by the interviewer into the data collection site and system allows these data to be appended to the RSVP answers previously provided by the participant.

PRO Tool forms that have been filled out by the patient and uploaded to Engage Health will be pseudoanonymized as described above and sent to Inozyme for scoring via secure data transfer system or encrypted e-mail.

The electronic records reside on secure encrypted servers that are wholly owned by Engage Health. All data collected will be pseudoanonymized as described above, stored in a locked / secure location and stored on secure wholly-owned servers for a period of time consistent to permit study-related monitoring, audits, and analysis by providing direct access to all study records.

Despite the fact that Engage Health is not a covered entity under HIPAA, appropriate administrative, technical, and physical safeguards to protect the privacy of protected health information are employed at all times.

To review the privacy and data storage policies of Engage Health Inc. and a discussion of HIPAA compliance, study participants may visit <http://www.engagehealth.com/privacy-policy/> or contact the Data Privacy Officer at dataprivacyofficer@engagehealth.com.

Study participants will be notified that the Institutional Review Board (IRB) may inspect study records as part of its auditing program, but these reviews will only focus on the researchers and not on their responses, their personal information or involvement.

Number of participants (planned):

Target: 60; Minimum: 30; Maximum: 90. Study recruitment will be purposive, seeking to initially recruit 60 respondents, 20 respondents from each of the three groups with a minimum of 30 and maximum of 90;

60 participants across four groups; person or parent/legal guardian affected by ENPP1 (GACI or ARHR2) or the acute form of ABCC6 deficiency as described below;

- Acute infantile ENPP1 deficiency (note; due to the high infant mortality, this group is likely to include parents of affected children, both living and deceased)
- Acute infantile ABCC6 deficiency (note; due to the high infant mortality, this group is likely to include parents of affected children, both living and deceased)
- Progressive pediatric ENPP1 deficiency who are still growing (note; due to the age of those who are still growing, this group is likely to include parents of affected children)
- Adult ENPP1 deficiency who are no longer growing (note: due to the age of those who are no longer growing, this group is likely to include both patients \geq age 18 years and parents of affected children who are $<$ age 18 years or who are unable to answer for themselves)

In order to get a geographic sampling, the respondents will be recruited from countries where individuals speak English, French or German (likely to be the US, Germany, the UK, Canada, Australia and France).

Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Participant must be a person with ENPP1 deficiency or the acute infantile form of ABCC6 deficiency who is 18 years or older
or
2. The parent/caregiver of a patient who has been diagnosed with ENPP1 deficiency or the acute infantile form of ABCC6 deficiency. Please note, parents/caregivers of patients with ENPP1 deficiency who have passed away may participate
3. Confirmed diagnosis of ENPP1 deficiency or ABCC6 deficiency with written proof of disease provided
4. Ability to participate in the RSVP and interview in German, French or English, irrespective of country of residence.

<p>5. Able to grant informed consent</p> <p>6. Willing to participate in a 40-to-60-minute telephone interview, including follow up questions (if necessary)</p> <p>Exclusion Criteria</p> <p>1. Inability to meet any of the inclusion criteria</p>
<p>Investigational product, dosage, and mode of administration:</p> <p>Not applicable</p>
<p>Duration of study</p> <p>This is a one-year study. Each participant will participate in a single interview. Recruitment of participants and caregivers to be interviewed, and the start of the interviewing process should begin in 2Q 2020 and complete in 4Q 2020. Analysis and report should be completed by 4Q 2020.</p>
<p>Participating countries</p> <p>Any patient who can speak English, German or French. (Likely patients to reside in Germany, France, Australia, the UK, Canada, and the U.S.)</p>
<p>Name, Address and Phone of Sponsor's Medical Expert / Principal Investigator:</p> <p>Pedro Huertas, MD, PhD Chief Medical Officer Inozyme Pharma Inc. 280 Summer Street Boston, MA 02210</p> <p>Phone: +1.857.800.0356 Mobile: +1.978.394.5700 Email : pedro.huertas@inozyme.com Web : www.inozyme.com</p>
<p>Statistical methods:</p> <p>The data for each question in the study will be analyzed and reported by Engage Health using descriptive statistics as appropriate for the nature of the data collected—frequency distributions, cross-tabulations, and measures of central tendency and dispersion.</p>

Study risks:

This research study is not associated with any known risks; Time to complete the RSVP and interview may be as a possible inconvenience. Each respondent will need up to approximately 60 minutes for the entire process; 20 minutes to complete the RSVP including uploading the proof of ENPP1 deficiency or ABCC6 deficiency diagnosis, and approximately 40 minutes to complete the interview and address any follow-up questions if needed.

While Engage Health makes every reasonable effort to protect the information it collects study participants will be made aware there is always some risk involved when submitting Personal Data over the internet. We cannot guarantee that the RSVP site and servers are 100% safe from illegal tampering or “hacking.” However, once Study Data is received at Engage Health and entered into the database, any data submitted has the same protection that Engage extends to its own confidential information.

Study benefits:

Research participants may not benefit directly from this research; however, it is hoped that participation in the study will provide a better medical understanding of the ways that ENPP1 deficiency and acute ABCC6 deficiency disease impacts families in terms of disease burden and quality of life.

